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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/005,228	12/03/2001	Karen M. Lyons	22058-554	7961

7590 06/17/2005

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EXAMINER	
MARVICH, MARIA	

ART UNIT	PAPER NUMBER
1636	

DATE MAILED: 06/17/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/005,228	LYONS ET AL.	
	Examiner	Art Unit	
	Maria B. Marvich, PhD	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 March 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-27 and 32* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-27 and 32* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *03 December 2001* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

This office action is in response to an amendment filed 9/27/04. Claims 28-31 and 33-38 have been cancelled. Claims 1-27 and 32 are pending.

Response to Amendment

Any rejection of record in the previous action not addressed in this office action is withdrawn. There are no new grounds of rejection herein and therefore, this action is final.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-27 and 32 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. **This rejection is maintained for reasons of record in the office action mailed 3/25/04 and restated below.**

The test of enablement is whether one skilled in the art could make and use the claimed invention from the disclosures in the patent coupled with information known in the art without undue experimentation (*United States v. Telectronics, Inc.*, 8 USPQ2d 1217 (Fed. Cir. 1988)). Whether undue experimentation is required is not based on a single factor but is rather a conclusion reached by weighing many factors (See *Ex parte Forman*, 230 USPQ 546 (Bd. Pat.

App. & Inter, 1986) and In *re Wands*, 8USPQ2d 1400 (Fed. Cir. 1988); these factors include the following:

1) **Nature of invention**. The invention recites a method for reducing the severity of bone fractures, reducing the incidence of a bone fracture and a method for treating osteoporosis in a subject by administration of an agent that inhibits BMP-3 activity or expression. The invention utilizes a combination of molecular biology and clinical techniques.

2) **Scope of the invention**. Applicants recite that an inhibiting agent can be anti-BMP-3 antibody or an anti-BMP-3 antisense RNA, which are administered to a subject therapeutically. The steps of gene and antibody therapy exacerbate a complex method.

3) **Number of working examples and guidance**. Applicants have generated BMP-3 deficient mice to analyze BMP-3 function *in vivo*. These mice exhibited no skeletal deformities and increased bone density. Therefore, applicants propose that they have devised a treatment for reducing the severity of bone fractures, reducing the incidence of a bone fracture and a method for treating osteoporosis in which a subject is provided an agent that inhibits BMP-3 expression or activity. The specification discloses that an agent that inhibits BMP-3 activity can be an antibody or a receptor fragment of activin, a BMP-3 receptor. Agents with the potential to inhibit BMP-3 expression include anti-BMP-3 antisense molecules, ribozymes and peptide nucleic acids (PNA). The specification provides guidance for the technical aspect of generating any of these broad classification agents (pages 7, line 24 through page 26, line 14). Guidelines for pharmaceutically acceptable formulations, carriers and matrix are provided (see page 28, line 22 through page 30, line 8). Means of administration, dosage, formulations and regimens guidance is provided (pages 30, line 9 and pages 33, line 16). However, this guidance is general

and broad. Applicants have provided no *in vitro* or *in vivo* experimental systems to demonstrate or indicate that application of any specific inhibitor of BMP-3 expression or activity will result in said results.

4) **State of Art**. The application recites administration of antibodies to inhibit BMP-3 activity in a method that appears to require direct administration of the antibodies. The art of antibody therapy is an unpredictable art, which has been pursued for application to cancer treatment (see Halim, 1999). In this discipline, the right target, the right situation for treatment, the right mechanism and the right pairing of antibody and tumor type have eluded success (page 2, paragraph 5). Alternatively, the coding sequences of the antibodies can be administered as can the antisense molecules through gene therapy techniques. The art of gene therapy is also highly unpredictable. Three major obstacles for gene therapy are 1) gene expression 2) gene delivery and 3) efficacy and toxicity of administration (Meng and El-Diery, 1999). Vector based and non-vector based means of introducing the DNA into the cell to be expressed have not successfully overcome any of these obstacles.

The art of osteoporosis and osteoinduction treatment has typically been approached pharmaceutically with varied results (see page 2-3, Sambrook and Eisman, 2000). The use of gene therapy for the treatment of bone disease is being pursued as a potential application. However, the development of therapeutic targets is far from complete as is an understanding as to the exact nature of bone disease (see page 679, last three sentences, Cho and Nuttal, 2002). To date, therapeutic treatment of bone fractures and disease by antibody or gene therapy is highly unpredictable. The state of art of each goal alone is complex and requires great skill in the art.

5) **Unpredictability of the art**. The unpredictability of the invention is high due to the lack of recited *in vitro* and *in vivo* methods for the inhibition of BMP-3 activity and expression. Applicants disclose that transgenic mice deficient in BMP-3 exhibit reduced skeletal defects. However, neither antibody nor antisense agents are analyzed *in vivo* and *in vitro* for effects on bone fractures or osteoporosis. The unpredictability of using the claimed invention for use in humans is further mitigated due to the lack of methods or processes for gene therapy delivery of the agents of the instant invention. Many parameters must be addressed for *in vivo* use and yet there are no methods or means disclosed in the specification such as delivery methods for the introduction of the agents into humans, means of preparing the agents for *in vivo* applications, whether the DNA or protein is to be introduced and means of introduction, the right target, the right situation for treatment, the right mechanism and the right pairing of antibody and cell type. No *in vitro* or animal models have been provided as evidence of success of treatment.

6) Summary. The invention recites a method reducing severity of bone fractures, reducing the incidence of bone fractures and treating osteoporosis in a subject using inhibitors of BMP-3 activity and expression. In view of the unpredictability of the art to which the invention pertains and the lack of established protocols and the inability to predict what agents will function to inhibit BMP-3: undue experimentation would be required to practice the claimed methods with reasonable expectation of success, absent a specific and detailed description in the specification. Given the above analysis of the factors which the courts have determined are critical in determining whether a claimed invention is enabled, it must be concluded that the skilled artisan would have had to have conducted undue, unpredictable experimentation in order to practice the claimed invention.

Response to Arguments- -35 USC 112, first paragraph

Applicants traverse the claim rejections under 35 U.S.C. 112, first paragraph for lack of enablement on pages 10-15 of the amendment filed 9/27/04. Applicants argue the following. 1) A demand for *in* vivo data to prove that applicants have taught how to use the claimed invention is improper. In support, applicants reference MPEP 2107.03 which teaches that the courts have found that the mere identification of a pharmacological activity of a compound that is relevant to an asserted pharmacological use satisfies the utility requirement. 2) Applicants outline the identification of BMP-3 as clinically relevant which data is present in the specification. This data consists of *in vitro* characterization of BMP-3 function as well as animal models that supports a role for BMP-3 in antagonizing bone growth. Applicants argue that knock-out mice such as BMP-3 are valuable tools for discovering function of genes and for identifying methods of treatments based upon the functions of the genes and aid in development of "cause-and-effect" relationship between the expression and function. 3) Applicants submit that on balance the Wands factors argue in favor of the enablement of the claimed methods because the biological reagents for use in the claims are wither known in the art or can be made using methods well known in the art, the level of skill of one in the art is high, the nature of the invention is not complex. Applicants state that bone morphogenetic proteins have been used to treat bone disorders for several years. Finally, applicants argue that experimentation required for testing agents is permissible if it is merely routine.

Applicants' arguments filed 9/27/04 have been fully considered but they are not persuasive. The requirement of 35 U.S.C. 112, first paragraph as to how to use the invention is

different from the utility requirement of 35 U.S.C. 101. According to the MPEP, "If an applicant has disclosed a specific and substantial utility for an invention and provided a credible basis supporting that utility, that fact alone does not provide a basis for concluding that the claims comply with all the requirements of 35 U.S.C. 112, first paragraph. For example, if an applicant has claimed a process of treating a certain disease condition with a certain compound and provided a credible basis for asserting that the compound is useful in that regard, but to actually practice the invention as claimed a person skilled in the relevant art would have to engage in an undue amount of experimentation, the claim may be defective under 35 U.S.C. 112, but not 35 U.S.C. 101." (see MPEP 2164.07). The instantly recited claims have not been rejected based upon a lack of utility but for lack of enablement.

Specifically, the instant claims have been rejected for lacking adequate teachings for use of the instantly recited method steps for *in vivo* gene therapy. The invention as disclosed does not provide the skilled artisan with the ability to make or use the compositions and methods to reduce the severity of a bone fracture, reduce the incidence of a bone fracture, treat osteoporosis or antagonizing BMP-2 in a host. Contrary to the characterization of the state of the art, the methods of the instant invention require more than generating the compositions to be administered. Rather, the compositions must then be administered such that the severity or incidence of a bone fracture or osteoporosis is reduced or BMP-2 is antagonized. The state of the art of gene and antibody therapy is high.

Applicants have demonstrated a casual role for BMP-3 in bone density by using knockout mice lacking BMP-3. The knock-out mice achieve complete lack of BMP-3 expression and activity. However, the claims are drawn to methods of inhibiting the activity or expression of a

BMP-3 polypeptide in a host which results cannot be extrapolated from the knock-out mice. These methods require administration of compounds that function to inhibit BMP-3. It is unknown if compounds can be administered in sufficient quantities or if they can be retained in the proper location in order to mediate inhibition. Therefore, the unpredictability of the art is high. In view of the unpredictability of the art to which the invention pertains, the high state of the art and the lack of established protocols and the inability to predict what agents will function to inhibit BMP-3: undue experimentation would be required to practice the claimed methods with reasonable expectation of success, absent a specific and detailed description in the specification

Conclusion

No claims are allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Maria B. Marvich, PhD whose telephone number is (571)-272-0774. The examiner can normally be reached on M-F (6:30-3:00).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Remy Yucel, PhD can be reached on (571)-272-0781. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Maria B Marvich, PhD
Examiner
Art Unit 1636

June 7, 2005.

JAMES KETTER
PRIMARY EXAMINER